CLAIMS

1. A chemical construct for use in solid phase synthesis comprising a solid support Q having linked thereto via a connecting group Y a substrate R; the connecting group Y having first and second cleavage sites which are orthogonally and selectively cleavable; the second cleavage site being selectively cleavable to release the substrate; and the first cleavage site being located at a position between the second cleavage site and the solid support and being selectively cleavable to release a fragment Fr comprising the substrate and at least a portion of the connecting group Y; characterised in that cleavage of the skeleton of the construct at the first cleavage site forms or introduces on the chemical fragment Fr at the first cleavage site a moiety comprising a sensitising group G which sensitises the chemical fragment Fr to instrumental, e.g. mass spectroscopic, analysis.

2. A chemical construct according to claim 1 wherein the chemical fragment Fr contains a means for imparting a characteristic signature to the mass spectrum of the fragment.

3. A chemical construct according to claim 2 wherein the characteristic signature is provided by incorporating into the fragment Fr a peak splitting isotopic label.

4. A chemical construct according to claim 3 wherein the peak splitting isotopic label is defined one or more isotope pairs selected from $^{1}H/H^{2}$ (D), $^{79}Br/^{81}Br$, $^{12}C/^{13}C$, $^{14}N/^{15}N$ and $^{16}O/^{18}O$.

5. A chemical construct according to any one of claims 2 to 4 wherein the means for imparting a characteristic signature to the mass spectrum of the fragment is located between the first and second cleavage sites.

6. A chemical construct according to any one of the preceding claims wherein the first and second cleavage sites cleavage sites are defined by first and second linker groups L^1 and L^2.

7. A chemical construct according to claim 6 wherein an spacer group A is interposed between the two linker groups L^1 and L^2, the spacer group A containing means for imparting a characteristic signature to the mass spectrum of the fragment Fr as defined in any one of claims 2 to 5.

8. A chemical construct according to claim 7 wherein the wherein the connecting group Y has the formula L^1-A-L^2.

9. A chemical intermediate construct according to claim 8 wherein the group A has the general formula NH-Alk-NH-X^1 wherein X^1 is hydrogen or an aralkyl group, and Alk is an alkylene group.

10. A chemical construct according to any one of the preceding claims wherein the sensitising group G is an ionisable group which is ionisable under mass spectrometric conditions.

11. A chemical construct according to claim 10 wherein the group G is ionisable to form a positive ion under mass spectrometric conditions, for example electrospray mass spectrometric conditions.

12. A chemical construct according to any one of the preceding claims wherein the group G is a basic amino group.

13. A chemical construct according to claim 12 wherein the basic amino group is a primary amino group.

14. A chemical construct according to claim 12 wherein the basic amino group is a tertiary amino group.

15. A chemical construct according to claim 14 wherein the tertiary amino group is a cyclic amino group.

16. A chemical construct according to claim 15 wherein the cyclic amino group is N-methylpiperazino.

17. A chemical construct according to claim 12 or claim 13 wherein the basic amino group is derived from the photochemical cleavage of a carbamate group.

18. A chemical construct according to any one of claims 3 to 17 wherein the peak splitting isotopic label is contained within a substituted or unsubstituted alkylene diamine group.

19. A chemical construct according to claim 18 wherein the alkylene diamine group is substituted by an N-benzyl group.

20. A chemical construct according to claim 19 wherein the N-benzyl group has a methylene group which is substituted with the peak splitting atom deuterium.

21. A chemical construct according to any one of the preceding claims wherein the first cleavage site is selectively cleavable by one type of chemistry selected from a group of chemistries consisting of cleavage under acid conditions, base catalysed cleavage, oxidative cleavage, reductive cleavage, nucleophilic displacement, cleavage by 1,2 *bis* nucleophiles, electrophilic displacement, and thermal, photochemical and enzymatic cleavage, and the second cleavage site is selectively cleavable by a different type of chemistry selected from the said group.

22. A chemical construct according to claim 21 wherein the first cleavage site is cleavable by one type of chemistry selected from:

(i) photochemical cleavage, e.g. photochemical cleavage of a nitrobenzylcarbamate group;

(ii) oxidation followed by cleavage through nucleophilic displacement, for example oxidation of a thiopyrimidine followed by nucleophilic displacement by an amine (e.g. a secondary amine such as N-methyl piperazine);

(iii) cleavage of a sulphonamide by nucleophilic displacement, for example by a thiolate nucleophile (e.g. mercaptoethanol I the presence of a strong base such as DBU);

(vi) cleavage of enamine groups (particularly those containing an enamine moiety conjugated to a carbonyl group; e.g. as 1-[4,4-dimethyl-2,6-dioxo-cyclohexylidene]ethyl amino) with a 1,2-*bis* nucleophile such as hydrazine or hydroxylamine or derivatives thereof ; and

(vii) transition metal catalysed cleavage of allyloxycarbonylamino groups, for example palladium (0) catalysed cleavage of allyloxycarbonylamino groups.

23. A chemical construct according to claim 22 wherein the second cleavage site is cleaved under acid conditions or by photolysis.

24. A chemical construct according to claim 21 or claim 22 wherein the first cleavage site is defined by a sulphonamide linker group, and the second cleavage site is optionally defined by a group, such as a Rink linker, which is cleavable under acidic conditions.

25. A chemical construct according to claim 21 or claim 22 wherein the first cleavage site is defined by a thiopyrimidine linker susceptible to cleavage by oxidation followed by nucleophilic displacement, and the second cleavage site is optionally defined by a group, such as a Rink linker, which is cleavable under acidic conditions.

26. A chemical construct according to claim 21 or claim 22 wherein the first cleavage site is defined by a dde group and the second cleavage site is optionally defined by a group, such as a Rink linker, which is cleavable under acidic conditions.

27. A chemical construct according to claim 21 or claim 22 wherein the first cleavage site is cleavable under photochemical conditions and the second cleavage site is defined by a group, such as a Rink linker, which is cleavable under acid conditions.

28. A chemical construct according to claim 21 or claim 22 wherein the first cleavage site is defined by a group such as allyloxycarbonylamino that can be cleaved by a transition metal such as palladium (0), and the second cleavage site is optionally defined by a group, such as a Rink linker, which is cleavable under acidic conditions

29. A chemical construct according to claim 21 or claim 22 wherein the first cleavage site is cleaved by oxidation followed by nucleophilic displacement.

30. A chemical construct according to claim 29 wherein the nucleophile is an amine.

31. A chemical construct according to claim 30 wherein the amine is a cyclic amine such as piperidine.

32. A chemical construct according to any one of the preceding claims wherein the fragment Fr contains a chromophore C^u that facilitates analysis of the fragment Fr by ultraviolet, visible or fluorescence spectrophotometry.

33. A chemical construct according to claim 32 wherein the chromophore C^u has a principal log E_{max} value of at least 2.5.

34. A chemical construct according to claim 33 wherein the principal log E_{max} value is at least 1.5 times greater than the principal log E_{max} of the substrate R.

35. A chemical construct according to any one of claims 1 to 34, the construct comprising a solid support Q having linked thereto via the connecting group Y the substrate R wherein the fragment Fr comprises the substrate and at least a portion of the connecting group Y, and the said portion contains a chromophore C^u which facilitates analysis of the fragment Fr^u by ultra violet, visible or fluorescence spectroscopy, the chromophore C^u having a principal log E_{max} value of at least 2.5 and wherein (i) the principal log E_{max} value is at least 1.5 times greater than the principal log E_{max} of the substrate R; or (ii) , the chromophore C^u has an absorption peak at a wavelength remote from absorptions due to the substrate R.

36. A chemical construct according to any one of claims 1 to 35 comprising a solid support Q having linked thereto via the connecting group Y the substrate R wherein the fragment Fr comprises the substrate and at least a portion of the connecting group Y, and the said portion contains a chromophore C^u which facilitates analysis of the fragment Fr^u by ultra violet, visible or fluorescence spectroscopy, wherein the absorption characteristics of the chromophore C^u and the substrate R are such that at a given measurement wavelength, any errors in measurement of the quantity of substrate R (or any fragment or construct containing the fragment) arising from any overlap between absorption bands due to the chromophore and absorption bands due to the substrate R are less than 10%, preferably less than 5%.

37. A chemical construct according to any one of claims 32 to 36 wherein the chromophore is a group containing an aryl group.

38. A chemical construct according to claim 37 wherein the aryl group is a fused polycyclic aryl group, in which one or more ring carbon atoms are optionally replaced by a heteroatom.

39. A chemical construct according to claim 38 wherein the fused polycyclic aryl group is selected from the group consisting of naphthyl, phenanthrenyl and

anthracenyl groups.

40. A chemical construct according to claim 39 wherein the fused polycyclic aryl group is an anthracenyl group.

41. A chemical construct according to claim 39 wherein the fused polycyclic aryl group is a dansyl (1-dimethylamino-5-naphthylsulphonyl) group.

42. A method of analysing the constructs of any one of the preceding claims; the method comprising cleaving the construct at the first cleavage site to release the chemical fragment Fr, the cleavage reaction generating on the chemical fragment Fr at the cleavage site a group comprising a mass spectrometric sensitising group G (e.g. a group which is ionisable under mass spectroscopic conditions), and then subjecting the chemical fragment to mass spectrometry, e.g. electrospray mass spectrometry.

43. An intermediate chemical construct for use preparing a chemical construct as defined in any one of the preceding claims, the intermediate construct having the formula Q-Y' wherein Q' is a reactive or protected form of the group Q.

44. An intermediate construct of the formula $Q\text{-}L^1\text{-}A^P$ wherein Q and L^1 are as defined in any one of the preceding claims and A^P is a reactive or protected form of the spacer group A containing a peak splitting isotopic label.

45. An intermediate construct according to claim 44 having the general formula $Q\text{-}L^1\text{-}NH\text{-}Alk\text{-}NH\text{-}X^1$ wherein X^1 is hydrogen or an aralkyl group, and Alk is an alkylene group.

46. A method of analysis of a solid phase construct; which method comprises:

(i) providing a chemical construct comprising a solid support Q having linked thereto via a connecting group Y a substrate R wherein Q, Y and R are as defined in any one of the preceding claims; the connecting group Y having first and second cleavage sites which are orthogonally and selectively cleavable; the second cleavage site being selectively cleavable to release the substrate; and the first cleavage site being located at a position between the second cleavage site and the solid support and being selectively cleavable to release a fragment Fr comprising the substrate and at least a portion of the connecting group Y, wherein

the said portion contains a chromophore C^u which facilitates analysis of the fragment Fr^u by ultra violet, visible or fluorescence spectrophotometry;

(ii) cleaving the connecting group at the first cleavage site to release the fragment Fr; and

(iii) subjecting the fragment Fr to ultra violet, visible or fluorescence spectrophotometric analysis to quantify the substrate R.

47. A method of analysis of a solid phase construct; which method comprises:

(i) providing a chemical construct comprising a solid support Q (e.g. a resin bead having an average diameter in the range from 90μm to 250μm) having linked thereto via a connecting group Y a substrate R wherein Q, Y and R are as defined in any one of the preceding claims, the substrate R being present on each solid support in an amount of no more than 10 nanomoles, preferably less than 5 nanomoles and more preferably less than 2 nanomoles; the connecting group Y having first and second cleavage sites which are orthogonally and selectively cleavable; the second cleavage site being selectively cleavable to release the substrate; and the first cleavage site being located at a position between the second cleavage site and the solid support and being selectively cleavable to release a fragment Fr comprising the substrate and at least a portion of the connecting group Y, wherein the said portion contains a chromophore C^u which facilitates analysis of the fragment Fr by ultra violet, visible or fluorescence spectrophotometry;

(ii) isolating a solid support, or a plurality of solid supports not exceeding 20 in number (preferably less than 10, more preferably less than 5, e.g. 1 solid support);

(iii) treating the solid support(s) to cleave the connecting group at the first cleavage site to release the fragment Fr^u containing the substrate R; and

(iv) subjecting the fragment Fr^u to ultra violet, visible or fluorescence spectrophotometric analysis to quantify the substrate R.

48. A method of identifying a pharmaceutically useful substrate comprising preparing a library containing a plurality of chemical constructs as defined in any of the preceding claims, and subjecting the library to biological testing to identify biologically active substrates.

49. A method according to claim 48 that includes the further step of formulating a biologically active substrate thus identified with a pharmaceutically acceptable

carrier to form a pharmaceutical composition.

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